

**REMARKS**

Claims 1-43 are pending.

Substitute paper and original computer readable forms of the Sequence Listing are being submitted herewith in response to the requirement under 35 U.S.C. 371 to comply with the Sequence Rules 37 CFR § 1.821 et seq. The attached substitute paper and original computer readable forms of the Sequence Listing do not add new matter, and their contents are the same. Typographical errors in the length of SEQ ID NOS:1 and 7 have been corrected. Prompt notice of any defects in the Sequence Listing is earnestly solicited and additional time is requested to comply.

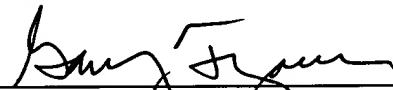
A statement claiming priority under 35 U.S.C. 371 is added after the title. Furthermore, errors in the specification are being corrected.

Applicants earnestly solicit an early examination on the merits. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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**APPENDIX**  
**MARKED-UP VERSION TO SHOW CHANGES**

**IN THE SPECIFICATION**

The following new paragraph is added on page 1 after the title:

This is a national stage application under 35 U.S.C. 371 of PCT/JP00/01041, filed on February 23, 2000, now abandoned.

The specification is amended as follows.

Page 8, first paragraph starting on line 1,

(12) The DNA according to the above (4) wherein the DNA encoding a polypeptide having  $\beta$ -ketoacyl-ACP synthase activity is:

a DNA comprising the nucleotide sequence selected from the group consisting of nucleotide Nos. 1441-2742, 6256-7545, 12076-13368, 15217-16506, 20008-21297 and 24781-26079 of SEQ ID NO: 1, and nucleotide Nos. 100-1383, 4771-6060, 7906-9258, 14935-16224, 20413-21705 and 25810-27102 of [SEQ ID NO:1] SEQ ID NO: 2; or

a DNA which hybridizes with this DNA under stringent conditions and which encodes a polypeptide having  $\beta$ -ketoacyl-ACP synthase activity.

Page 11, fifth paragraph starting on line 29 and continuing to page 12,

(26) A DNA comprising the nucleotide sequence selected from the group consisting of nucleotide Nos. 1441-2742, 6256-7545, 12076-13368, 15217-16506, 20008-21297 and 24781-26079 of SEQ ID NO: 1, and nucleotide Nos. 100-1383, 4771-6060, 7906-9258, 14935-16224, 20413-21705, and 25810-27102 of [SEQ ID NO: 1] SEQ ID NO: 2; or

a DNA which hybridizes with this DNA under stringent conditions and which encodes a polypeptide having  $\beta$ -ketoacyl-ACP synthase activity.

Page 13, fourth paragraph starting on line 21 and continuing to page 14,

(33) A polypeptide comprising the amino acid sequence selected from the group consisting of amino acid Nos. 29-344, 366-451, 481-914, 1050-1356, 1715-1892, 1979-2060, 2086-2515, 2983-3128, 3537-3714 and 3805-3886 of SEQ ID NO: 3, amino acid Nos. 36-466, 596-908, 978-1059, 1083-1512, 1653-1964, 2306-2483, 2575-2656, 2680-3109, [32030-3538] 3230-3538, 3878-4056, 4159-4240, 4271-4703, 4815-5122, 5168-5307, 5753-5930 and 6032-6113 of SEQ ID NO: 4, amino acid Nos. 34-461, 550-891, 1212-1396, 1483-1564, 1591-2020, 2108-2448, 2525-2606, 2636-3086, 3226-3591, 3629-3763, 4183-4363, 4460-4553 and 4627-4873 of SEQ ID NO: 5, amino acid Nos. 38-467, 574-914, 956-1081, 1488-1673, 1756-1837, 1864-2294, 2390-2732, 2776-2902, 3288-3473, 3556-3637, 3663-4093, 4182-4523, 4565-4685, 5085-5270 and 5353-5434 of SEQ ID NO: 6; or a polypeptide comprising an amino acid sequence wherein one or more amino acids are deleted, replaced or added in the amino acid sequence selected above, and having avermectin aglycon synthase domain activity.

Page 24, fourth paragraph starting on line 25 and continuing to page 25,  
in SEQ ID NO: 4,  
KS3: 36 to 466,  
AT3: 596 to 908,  
ACP3: 978 to 1059,  
KS4: 1083 to 1512,  
AT4: 1653 to 1964,  
KR4: 2306 to 2483,  
ACP4: 2575 to 2656,  
KS5: 2680 to 3109,  
AT5: [32030 to 3538] 3230 to 3538,  
KR5: 3878 to 4056,  
ACP5: 4159 to 4240,  
KS6: 4271 to 4703,  
AT6: 4815 to 5122,

DH6: 5168 to 5307

[DH6: 5753 to 5930] KR6: 5753 to 5930,

ACP6: 6032 to 6113;

Page 26, third paragraph starting on line 21,

In other words, based on the above module, domain and ORF information obtained from DNAs having nucleotide sequences of SEQ ID NO: 1 and 2 derived from *Streptomyces avermitilis*, modules, domains and ORFs, which are relevant to the Avermectin aglycon synthase genes [of the present invention] derived from other bacteria capable of producing avermectin, can be determined.

Page 35, first paragraph starting on line 1,

Specific examples include SP2/O, NSO and the like for mouse myeloma cells, YB2/O and the like for rat myeloma cells, HEK293 (ATCC: CRL-1573)[, 293] and the like for human fetal kidney cells, BALL-1 and the like for human leukemia cells, and COS-1, COS-7 and the like for African green monkey kidney cells.

Page 43, fifth paragraph starting on line 22,

Examples of the thus obtained protein include a protein comprising [the amino acid sequence represented by SEQ ID NO:1] the amino acid sequences represented by SEQ ID NOS:3, 4, 5 and 6.

Page 43, sixth paragraph starting on line 25 and continuing to page 44,

Furthermore, a fusion protein of the protein of the present invention and other protein may be produced, and purified by affinity chromatography using a substance having affinity to the fusion protein. For example, the protein of the present invention may be produced as a fusion protein with protein A according to the method of Lowe *et al.* (*Proc. Natl. Acad. Sci. USA*, 86: 8227 (1989); *Genes Develop.*, 4: 1288 (1990)), or the method described in Japanese Published Unexamined Patent Application No.

336963/93 or [823021/94] WO 94/23021, and purified by affinity chromatography using immunoglobulin G.

### **IN THE CLAIMS**

The claims are amended as follows.

12. (Amended) The DNA according to claim 4 wherein the DNA encoding a polypeptide having  $\beta$ -ketoacyl-ACP synthase activity is:  
a DNA comprising comprising the nucleotide sequence selected from the group consisting of nucleotide Nos. 1441-2742, 6256-7545, 12076-13368, 15217-16506, 20008-21297 and 24781-26079 of SEQ ID NO: 1, and nucleotide Nos. 100-1383, 4771-6060, 7906-9258, 14935-16224, 20413-21705 and 25810-27102 of [SEQ ID NO: 1] SEQ ID NO: 2; or  
a DNA which hybridizes with said DNA under stringent conditions and which encodes a polypeptide having  $\beta$ -ketoacyl-ACP synthase activity.

26. (Amended) A DNA comprising the nucleotide sequence selected from the group consisting of nucleotide Nos. 1441-2742, 6256-7545, 12076-13368, 15217-16506, 20008-21297, and 24781-26079 of SEQ ID NO: 1 and nucleotide Nos. 100-1383, 4771-6060, 7906-9258, 14935-16224, 20413-21705 and 25810-27102 of [SEQ ID NO: 1] SEQ ID NO: 2; or  
a DNA which hybridizes with said DNA under stringent conditions and which encodes a polypeptide having  $\beta$ -ketoacyl-ACP synthase activity

33. (Amended) A polypeptide comprising the amino acid sequence selected from the group consisting of amino acid Nos. 29-344, 366-451, 481-914, 1050-1356, 1715-1892, 1979-2060, 2086-2515, 2983-3128, 3537-3714 and 3805-3886 of SEQ ID NO: 3, amino acid Nos. 36-466, 596-908, 978-1059, 1083-1512, 1653-1964, 2306-2483, 2575-2656, 2680-3109, [32030-3538] 3230-3538, 3878-4056, 4159-4240, 4271-4703, 4815-5122, 5168-5307, 5753-5930 and 6032-6113 of SEQ ID NO: 4, amino acid

Nos. 34-461, 550-891, 1212-1396, 1483-1564, 1591-2020, 2108-2448, 2525-2606, 2636-3086, 3226-3591, 3629-3763, 4183-4363, 4460-4553 and 4627-4873 of SEQ ID NO: 5, amino acid Nos. 38-467, 574-914, 956-1081, 1488-1673, 1756-1837, 1864-2294, 2390-2732, 2776-2902, 3288-3473, 3556-3637, 3663-4093, 4182-4523, 4565-4685, 5085-5270 and 5353-5434 of SEQ ID NO: 6; or  
a polypeptide comprising an amino acid sequence wherein one or more amino acids are deleted, replaced or added in the amino acid sequence selected above, and having avermectin aglycon synthase domain activity.

**IN THE SEQUENCE LISTING**

The substitute paper and original computer readable forms of the Sequence Listing are attached.

09/914,286